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# Natural Compounds as an Alternative to Control Farm Diseases: Avian Coccidiosis

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## Abstract

Coccidiosis is one of the most aggressive and expensive parasite diseases in poultry industry worldwide. Currently, the most used control techniques are chemoprophylaxis and anticoccidial feed additives. Although there is a great variety of commercial anticoccidial drugs and vaccines in the market, there is also a significant resistance to use them in animals with human as final consumer. To date, none available product offers effective protection toward coccidiosis; however, the search for novel strategies to control this disease continues, and natural products have arisen as a potential way to cope with avian coccidiosis. In this chapter, we highlight recent advances in natural compounds, their anticoccidial properties, and mechanisms.

**Keywords:** chickens, coccidiosis, *Eimeria*, anticoccidial, natural products

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## 1. Introduction

Chicken is considered an animal food with high consumption around the world; so, the development of novel drugs and vaccines to cope with poultry diseases is essential for worldwide food safety. Today, investment on poultry research is focused on development of anticoccidial treatments that can control pathogens at different stages of growth. Avian coccidiosis is an intestinal disease caused by apicomplexan protozoa belonging to genus *Eimeria* and is considered the most economical important parasitic disease affecting poultry industry globally [1–3].

The study of *Eimeria* spp. has driven the search of new chemical or natural compounds in order to control infections, which may be caused by even more than one species that infect different regions of the chicken intestine. In addition, some other environmental and non-environmental factors can contribute to dispersion of *Eimeria* oocysts, such as *Eimeria* virulence, high oocyst

challenge, poor ventilation, high stocking density, low immune status of the host, bacterial enteritis, high moisture levels in litters humidity and lower efficacy of anticoccidial drugs [4, 5].

Disease control includes vaccines, anticoccidial chemicals, coccidiostats, ionophores, probiotics, natural extracts, and natural compounds. However, the constant use of antibiotics induces selection of multidrug-resistant strains of parasites, besides the fact that drug residues may remain in poultry products for human consumption. This is why animal health regulations were established; for example, in European countries, prophylactic control based on mixtures of food with anticoccidial additives has been strongly limited since 2006 and they withdraw from the market in 2021 (Council Directive of 2011/50/EU of the European Council) [3, 6].

To cope with this situation, vaccination is the only preventive method that may help to control avian coccidiosis. In this regard, the use of natural compounds may be considered as an effective way to control coccidiosis in combination with integrated pest management. Research of natural products and the use of derivatives of plants have potential since these new therapeutic molecules are unknown to *Eimeria* strains and therefore they have not yet developed resistance [7]. The natural products used to control avian coccidiosis include plants [4], prebiotics, probiotics [4, 8], and fungi [9, 10].

## 2. Coccidiosis in poultry industry

Commercial poultry farming is expanding daily, and poultry is the most efficient source of animal-derived protein [11]. Chicken meat is considered as an important source of animal proteins and fats, as well as a source of a whole range of organic and inorganic substances [12].

Worldwide, poultry generation has tripled in the last two decades, and the world's chicken herd is close to 21 billion, but annual production of new individuals is more than 60 billion and delivers more than 1.1 trillion eggs and more than 90 million tons of meat [13].

Chicken meat production is growing rapidly around the world, with a significant increase in the production. In a short period, between 2000 and 2012, the global chicken meat market increased more than 58.48%. Fifty years ago, 79% of the chicken market was absorbed for American and European countries, but currently, Asian and American countries contributed approximately 77% of total world production according to reports in 2014 [4, 14]. Differential growth in production has been observed according to geographical location as follows: The Asian's production had the largest increase with more than 68.83%, the African's production increased in 67.73%, the European's production increased in 65.82%, and the American's production with 47.67%. Currently, the world production is dominated by the USA, China, Brazil, Mexico, Russia, and India [4, 14]. The growing demand of meat is proportional to the increasing number of inhabitants in the world and their rising acquiring power, moreover, to the fact that chicken meat cost is cheaper than other kinds of meat [15].

The poultry industry is still confronted with many diseases like coccidiosis, an intestinal parasitic disease that is considered as one of the most aggressive diseases in poultry, causes strong economic losses, and causes damage in animal health and productivity. The global economic loss has been estimated up to 3 billion dollars worldwide including production losses, prevention, and

treatment costs [4, 13, 16, 17]. Losses are mainly due to morbidity as coccidiosis results in reduction in weight gain and egg production additionally to affect the quality of meat by diminishing feed conversion, malabsorption, and maldigestion and further leads to mortality [18]. The poultry industry operation requires that large groups of chickens are kept on the floor at high humidity in warm conditions, appropriate for the development and transmission of the avian coccidia; therefore, the development of novel and natural compounds that control this disease is imperative [19].

### 3. Etiologic agents of coccidiosis

In poultry, the principal etiologic agents of coccidiosis are obligatory intracellular protozoan parasites of the genus *Eimeria*, subclass Coccidia that belong to family Eimeriidae and the phylum Apicomplexa [2, 18, 20]. This phylum groups many other protozoa of medical and/or veterinary importance. It has been reported around 5000 species of apicomplexan parasites, including some that affect humans as malarial parasites *Plasmodium* spp.; the zoonotic organisms *Cryptosporidium parvum* and *Toxoplasma gondii*; *Babesia* and *Theileria* and the more recently described *Neospora caninum*, cattle parasites; and *Eimeria* spp., with host diversity as cattle and poultry pathogens [4, 18, 21]. The majority of apicomplexans are obligate intracellular parasites that infect new host cells by invasive extracellular stages, that involve a specialized array of cytoskeletal elements and secretory organelles known as the apical complex (micronemes, rhoptries, dense granules, and conoid and polar rings), and that would provide the structural stability necessary during the host invasion process [4, 18, 21, 22].

On the other hand, a single host species was reported for more 1200 *Eimeria* spp., and all of these are restricted to this single species [3, 23]. Also, close to ten *Eimeria* spp. have been reported that can infect *Gallus gallus* var. *domesticus*: *E. mitis* [26], *E. maxima* [26], *E. brunetti* [27], *E. acervulina* [24–26], *E. mivati* [28], *E. necatrix* [29], *E. praecox* [29], *E. tenella* [30], and *E. hagani* [31]. In chicken production, seven *Eimeria* spp. that are associated with clinical coccidiosis have been reported: *E. maxima*, *E. brunetti*, *E. acervulina*, *E. tenella*, *E. praecox*, *E. necatrix*, and *E. mitis*. Of all these, *E. tenella* causes significant economic losses; therefore, it is the most studied strain [32, 33].

### 4. Pathogenicity

*Eimeria* spp. can infect and duplicate inside the mucosal epithelia in several areas of bird by oral means. Subsequently, they cause gut harm (e.g., hemorrhage, diarrhea, inflammation, etc.), morbidity, and mortality in poultry [4, 5]. Each of which species of parasite causes disease. But the clinical signs vary according to the species, and their pathogenicity varies in birds of different genetic backgrounds in a range from mild damage to severe damage, i.e., are considered highly pathogenic: *E. tenella*, *E. maxima*, *E. necatrix*, and *E. brunetti* that has been well characterized in relationship of the neurotic conditions they create, furthermore, the gross lesions that are found in several areas of the gut, however, *E. mitis* and *E. acervulina* do not produce gross lesions or cause mortality in infected host, for their tissue trophism, therefore, are considered mildly pathogenic, whereas *E. praecox* is considered to be the least pathogenic, although in *Eimeria* high densities population levels can potentially cause illness (Table 1) [5, 33–35].

<i>Eimeria</i> species	Site of development	Oocyst size ( $\mu\text{m}$ )		Shape	Gross lesions	Pathogenicity	Ref.
		Length	Width				
<i>E. necatrix</i>	Jejunum, ileum, ceca	12–29	11–24	Ovoid	The intestine may be ballooned  The mucosa thickened and the lumen filled with fluid, blood, and tissue debris  Lesions in dead birds are observable as black and white plaques (schizont accumulations)	++++	[4, 29, 43, 44]
<i>E. tenella</i>	Ceca	14–31	9–25	Ovoid	Thickened cecal wall and bloody contents at the proximal end  Distension of cecum  Villi of the duodenum destruction causing extensive hemorrhage and death	++++	[4, 30, 43–45]
<i>E. brunetti</i>	Ceca, rectum	14–34	12–26	Ovoid	Inflammation of the intestinal wall with pinpointed hemorrhages  Sloughing of epithelia	++++	[4, 27, 43, 44]
<i>E. maxima</i>	Jejunum, ileum,	21–42	16–30	Ovoid	Inflammation of the intestinal wall with pinpointed hemorrhages  Sloughing of epithelia	+++	[4, 26, 43, 44]
<i>E. mitis</i>	Ileum	10–21	9–18	Subspherical	Limited enteritis causing fluid loss Malabsorption of nutrients	++	[4, 26, 43, 44]
<i>E. acervulina</i>	Duodenum, ileum	12–23	9–17	Ovoid	Limited enteritis causing fluid loss Malabsorption of nutrients  Small red spots and white bands  on the upper part of the small intestine	++	[4, 26, 43, 44]
<i>E. praecox</i>	Jejunum, duodenum	20–25	16–20	Ovoid	Watery intestinal contents  Mucus and mucoid casts	+	[4, 29, 43, 46]

**Table 1.** Important characteristics of *Eimeria* ssp. which are causative agent of coccidiosis.

## 5. Clinical signs and lesions

Birds infected with coccidiosis show signs like huddling, listlessness, diarrhea, loss of appetite, and weight loss [36]. Many *Eimeria* spp. are able to cause observable clinical signs to infected and unprotected birds; nevertheless, however, it is frequently determined by sub-clinical infections. These are often undervalued but frequently result in impaired feed conversion and reduced weight gain [37].

Young birds are more susceptible and easily display signs of disease; in contrast, older chickens are relatively resistant as a result of prior infection. The factors that influencing on the severity of infections are the number of *Eimeria* spp. sporulated oocysts ingested, age of birds, and immune and environmental status of the group; in addition, the contagion can be aggravated because the infected birds tend to huddle together, and droppings are whitish or bloody and watery, ending with dehydration and poor weight gain as well as mortalities [37].

Many different *Eimeria* spp. can infect several areas of the intestinal mucosa and infringe a degree of epithelial cell damage like inflammation [38]. The damage of coccidiosis infection is measured by the degree of inflammation and damage to the intestinal tract: petechial hemorrhages, necrosis, mucous profuse bleeding in the ceca, and mucoid to blood-tinged exudates (**Table 1**).

The tissue harm in the intestinal tract may permit other colonizations by different microorganisms, for example, *Clostridium perfringens* [39]. It has been reported that the infection for *Histomonas meleagridis* was more severe when combined with *E. tenella* [37, 40]. The damage leads to dehydration, diarrhea, dysentery, rectal prolapse, and death [41]. Moreover, each *Eimeria* sp. varies in infection location in the gastrointestinal tract (ranging from the duodenum to the cecum). For example, *E. mitis* infects in the middle part of the small intestine, *E. necatrix* infects in the small intestine, *E. acervulina* infects in the duodenum, *E. maxima* and *E. tenella* infect in the ceca, and *E. brunetti* develops in the ceca and the rectum (**Table 1**) [5, 33, 42].

## 6. Life cycle

The biological cycle of the protozoa of the genus *Eimeria* is similar to that of other protozoans of the coccidial type. They are obligate intracellular parasites that infect and develop in epithelial cells of the intestinal mucosa causing severe damage to the gut [47]. The life cycles of *Eimeria* spp. are complex, include three different phases, sporogony, merogony, and gametogony, and comprise both sexual and asexual reproductive phases [35, 48]. Some species vary in the number of asexual generations and in the time corresponding to every developmental stage [13, 49].

Infections begin when sporozoites are released from sporocyst and penetrate new cells. Once the sporozoite has achieved to penetrate into the epithelial cell, it forms the vacuola parasitofora and undergoes a process of rounding, transforming into a trophozoite. Then, by multiple nuclear divisions (so-called schizogony), the trophozoites become in the schizonts of the first generation. At the end of the maturation of the schizont, rupture of the membrane of the cell host allows the release of the merozoites to penetrate new cells [50].



These cycles of asexual schizogony (merogony) may be repeated numerous times. The sporozoites undergo merogony resulting in the release from one sporozoite of about 1,000 merozoites; occasionally, this stage is repeated two to four times and after sometimes merozoites develop into either male or female and form into host cell (gametogony, the sexual phase) [33, 50]. Microgametes (male) are flagellated and travel to the immobile macrogametes (female) to fertilize these stages. Upon fertilization, the wall-forming bodies of the macrogametes are externalized and fuse to form the oocyst wall of the unsporulated oocyst that is released from the intestinal mucosa and then is excreted with the feces [4, 33, 49–53].

Once the birds are infected, sporozoites are released within oocysts and penetrate new host cells in the intestinal mucosa, to invade and destroy them and initiate the life cell cycle. As a consequence, infected birds display symptoms of disease such as reduced feed intake, bloody diarrhea, hampered weight gain, loss of appetite, and huddling [2, 4, 36, 50, 54]. The complete process between oocyst ingestion and release may take between 4 and 6 days (depending on the species) [49].

Pathogenic species are typically characterized by at least one large endogenous life cycle stage, which may be asexual (e.g., second-generation schizont of *E. tenella* or *E. necatrix*) or gametocyte (e.g., *E. maxima*). The prepatent period usually fluctuates from 4 to 5 days after oral infection, and maximal oocyst output ranges from day 6 to 9 post-infection [52].

## 7. Modes of transmission

Coccidian parasites are transmitted by direct or indirect contact with the excrement of other infected birds; afterward a bird ingests coccidia, the organism invades the intestinal mucosa causing damages in the tissues as it reproduces [50, 55]. Following infection, coccidia produces immature oocytes, which are expelled with the fecal matter, usually in an unsporulated (no infective state) and cannot infect another bird unless they undergo a process of sporulation (infective state). Oocysts may remain in the environment for months to years, depending on the species and environmental conditions [50]. In the environment, sporozoites are protected from desiccation, as well as climatic conditions, such as cold, hot weather, and chemical disinfection by the oocyst wall. This structure assures successful disease transmission and is essential for the parasite survival in the environment [50, 55]. In this regard, it has been reported that in environmental conditions the sporulated oocyst can survive up to 602 days, while an unsporulated oocyst can survive up to 7 months in the cecal tissue [4, 33].

## 8. Coccidian oocysts

A defining characteristic of the *Coccidia* spp. is the development of resistant oocysts that are shed with feces. The coccidian oocyst are exogenous stages that are usually unsporulated in the feces and are considered a remarkably hard and persistent structure. It is resistant to mechanical and chemical damage and to proteolytic degradation. They are difficult to eliminate from the environment because they are surrounded by an indestructible wall that confers resistance to chemical disinfection [55–57].

Plant	Compound	Species	Life cycle stages	Reference
<i>Artemisia annua</i>	Artemisinin	<i>E. tenella</i>	Oocyst formation	[58, 59]
		<i>E. acervulina</i>	Sporulated	
		<i>E. máxima</i>		
<i>Pinus radiata</i>	Tannin	<i>E. tenella</i>	Sporulated	[60]
		<i>E. acervulina</i>		
		<i>E. máxima</i>		
<i>Azadirachta indica</i>	Bornyl acetate	<i>E. tenella</i>	Oocyst formation (immune modulation)	[61, 62]
	$\alpha$ -Pinene limonene			
	b-Caryophyllene			
<i>Sophora flavescens</i>	2-Ethyl-1-hexanol geranyl	<i>E. tenella</i>	Oocyst formation (immune modulation)	[63, 64]
		<i>E. acervulina</i>		
		<i>E. máxima</i>		
<i>Berberis lycium</i>	Berberine	<i>E. tenella</i>	Oocyst formation (immune modulation)	[65–67]
	Berberine palmitine	<i>E. acervulina</i>		
	Antocyanin berbamine	<i>E. maxima</i>		
<i>Origanum vulgare</i>	Thymol	<i>E. tenella</i>	Oocyst formation	[68, 69]
	Carvacrol	<i>E. acervulina</i>		
	$\gamma$ -Terpinene	<i>E. maxima</i>		
	p-Cymene			
<i>Pimpinella anisum</i>	p-Allylanisole	<i>E. tenella</i>	Sporulated	[58]
	Z-a-biosabolene			
<i>Allium sativum</i>	Allicin	<i>E. tenella</i>	Sporulated	[70]
<i>Bidens pilosa</i>	Polyacetylene	<i>E. tenella</i>	Oocyst formation (immune modulation)	[71]
<i>Linum usitatissimum</i>	N-3fatty acids	<i>E. tenella</i>	Schizogony	[72]
<i>Ageratum conyzoides</i>	Flavonoids	<i>E. tenella</i>	Schizogony	[73]
<i>Carica papaya</i>	Papain	<i>E. tenella</i>	Oocyst formation (immune modulation)	[74]
<i>Syzygium aromaticum</i>	Eugenol and eugenyl acetate	<i>E. tenella</i>	Sporulated	[75]
<i>Melaleuca alternifolia</i>	Terpinen-4-ol and gamma-terpinene	<i>E. oocyst</i>	Oocyst formation	[75]

**Table 2.** Anticoccidial activity of plants against *Eimeria* spp. and their target life cycle stage.



Commercial product	Composition	Supplier
Solucox	Vinegar of cider, macerates of red rose ( <i>Rosa gallica</i> ), white thyme ( <i>Thymus vulgare</i> ), goldenrod ( <i>Solidago virga aurea</i> ), oregano ( <i>Origanum vulgare</i> )	La Ferme de Beaumont
Elan Biotic®	Mixture of plant extracts, herbs, essential oils, organic acids, and tannins	Olus plus BV
Elan plus®	Mixture of plant extracts, herbs, essential oils, organic acids, and tannins	Olus plus BV
Necotyl®	Mixture of plant extracts, herbs, essential oils, organic acids, and tannins	Olus plus BV
Verm-X Poultry® Pellets	Wheat meal, wheatfeed meal, limestone flour, garlic, cinnamon, common thyme, seaweed meal, sunflower oil, nettle, cleavers, fennel, peppermint, slippery elm, quassia, dicalcium phosphate, cayenne	Verm-X
Verm-X Poultry® Liquid	Cinnamon, garlic, common thyme, peppermint, fennel, cleavers, nettle, slippery elm, quassia, elecampane	Verm-X
Cocci-Guard	Concentrated saponin extract	DPI Global
BP formulation	<i>Bidens pilosa</i> , and other plants	Ta Fong, Inc.
Alquernat Zycox	Mixture of plants <i>Holarrhena antidysenterica</i> , <i>Berberis aristata</i> , <i>Embelia ribes</i> , and <i>Acorus calamus</i> , polyphenols, essential oils, and polysaccharides	Biovet SA
Plant and extracts having anticoccidial activity	Mixture of <i>Quercus infectoria</i> , <i>Rhus chinensis</i> , and <i>Terminalia chebula</i>	Kemin Industries
Apacox	<i>Agrimonia eupatoria</i> , <i>Echinacea angustifolia</i> , <i>Embelia ribes</i> , <i>nigrum</i> , <i>Cinchona succirubra</i>	GreenVet
Avihicox	<i>Bocconia cordata</i> and clove extract	Centaur
Nutrimin	Apple cider vinegar	Chicken Licken
Kocci Free	Free olive leaf, mustard seed, black seed, cloves, grapefruit seed extract	Amber Technology
Oil of oregano factors	Oregano extra virgin olive oil (80% carvacrol)	Natural factors
Oilis	Natural vegetal extracts	Engormix
Oreganico	Oregano oil and essential oils	Flyte so fancy
Garlic	Garlic granules	Flyte So Fancy
Poultry ProVita	Probiotics and prebiotic inulin	Vets Plus
CitriStim®	CitriStim Mannan oligosaccharides and beta glucans	ADM
Orego-Stim®	Orego-Stim carvacrol (82%) and thymol (2.4%)	Saife VetMed
Herban	Etheric oils, soya oils, oregano oils	Uncle Ted's Organics Ltd.
Herb 'n' Thrive	Concentrated blend of herbs and essential oils	Chicken Licken
Eimericox®	Several essential oils (Phytosynthese/Trouw Nutrition)	Phytosynthese/Trouw Nutrition

Commercial product	Composition	Supplier
Natustat	Several essential oils and yeast cell walls	Alltech
EnteroGuard	Garlic and cinnamon	Orffa
Xtract Immunocox	Spanish pepper and turmeric	Pancosma
Coxynil	<i>Allium sativum</i> Linn 15%, <i>Cinnamomum camphora</i> Nees and Eberum 15%, <i>Elephantopus scaber</i> Linn 15%, <i>Valeriana wallichii</i> DC 15%, sulfur dioxide 25% and NaCl 15%	Growell India
Ropadiar® (powder and liquid)	Ethereal oil (oregano oil)	Ropapharm
Modified from [4].		

**Table 3.** Natural products available to control coccidiosis.

## 9. Prevention and control of coccidiosis

Avian coccidiosis is hard to eradicate by two principal reason: first, the oocyst wall is environmentally resistant and second, the sporulated oocyst can outlive for long time in the environment. Currently, controls strategies mainly depend on the use of anticoccidial drugs and live vaccines but the use of natural compounds to prevent avian coccidiosis go up daily [33].

These natural products can include plant extracts, probiotics. In poultry, mainly used as diet supplements with diverse effects as stimulation of immune response, anti inflammatory activities, cytoplasmic damage and antioxidant. By other hand, natural compounds from plant extracts possess metabolites with distinct mode of action capable to inhibiting different stages of the *Eimeria* species life cycle (**Tables 2 and 3**) [4, 7].

## 10. Conclusions

Coccidiosis is a frequent cause of diarrhea, morbidity, and mortality in domesticated birds, and notwithstanding a broad number of drugs to control this disease are commercially available. *Eimeria* species have developed resistance to conventional anticoccidial drugs over time. Due to widespread development of resistance and the increase of concern of consumers on food safety, different efforts have been made to search for new agents with anticoccidial activity. In this regard, the investigation on natural alternatives has grown quickly and has been considered the most effective and safe strategy for the control and prevention of coccidiosis. On the other hand, these new strategies are friendly with the environment, so that although they have a higher cost, the advantages that these offer are worth. Finally, recent advances in “omics” provide a novel approach for gene discovery involved in anticoccidial drug resistance and for developing marker-assisted selection strategies like method of disease prevention and control.

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